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COMPLETE SPECIFICATION

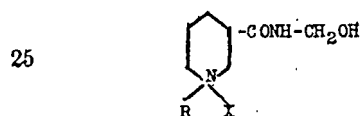
Novel Quaternary Nicotinic Acid Amide Derivatives and Production thereof

We, CILAG LIMITED, a Corporation organised under the Laws of Switzerland, of 209 Hochstrasse, Schaffhausen, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to novel quaternary nicotinic acid amide derivatives and to the production thereof.

We have found that the N-hydroxymethyl amide of nicotinic acid has an excellent curative effect on infections of the bile duct and the intestinal tract.

We have now found that by quaternising of the cyclic nitrogen atom of N-hydroxymethyl-nicotinic acid amide the effectiveness of this compound may be increased. The present invention accordingly provides a series of new therapeutically valuable compounds of the general formula:



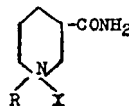
wherein R is an alkyl, carboxyalkyl, carbalkoxyalkyl or carbamidoalkyl group containing at most twenty carbon atoms and X is a halogen atom or an alkylsulphonate or alkoxyulphonate group containing at most six carbon atoms.

As already mentioned, these alcohols possess excellent germicidal properties and are intended for use as chemotherapeutics and as intermediate products.

35 The present invention also provides two processes suitable for the production of the new compounds of the above-men-

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tioned formula. According to the first of these processes formaldehyde is reacted 40 with compounds of the general formula:



in which R and X have the above-defined meanings. The two starting materials are preferably reacted together in a solvent. 45

According to the second process for the production of the new compounds, N-hydroxymethyl-nicotinic acid amide is reacted with compounds of the formula: R—X wherein R represents an alkyl, 50 carboxyalkyl, carbalkoxyalkyl or carbamidoalkyl group containing at most twenty carbon atoms and X represents a halogen atom, an alkylsulphonate group or an alkoxyulphonate group containing 55 at most six carbon atoms. The reaction may be carried out in the presence or absence of solvents.

In the nomenclature used throughout this specification and the appended claims 60 N₁ refers to the ring nitrogen atom and N to the nitrogen atom of the amide group.

The following examples show how the process of the invention may be carried 65 into effect:

EXAMPLE 1.

16 Gms. of N₁-chlor-N₁-methyl-nicotinic acid amide were suspended in 200 ccs. of ethanol and 10 ccs. of a neutralised 35% formaldehyde solution were added. The mixture was heated for an hour on the water bath and then allowed to cool. The hot solution was clear but on cooling and addition of acetone colourless crystals separated which were again re-crystallised from ethanol-acetone. N₁- 75

chlor - N₁ - methyl - N - hydroxymethyl - nicotinic acid amide was thus obtained in fine crystal clusters with a melting point of 160—161° C.

- 5 14 Gms. of the product were obtained corresponding to 69% of the theoretical yield. The compound is quite soluble in water and alcohol and sparingly soluble in ether, acetone and dioxane.

10 EXAMPLE 2.

- 15 43.7 Gms. of N-hydroxymethyl-nicotinic acid amide were suspended in 500 ccs. of dioxane and shaken in an autoclave for 25 hours with 60 gms. of methyl chloride at 100—120° C.

After cooling the mass crystallised out from the solution and was sucked off and washed with dioxane and ether. After recrystallisation from alcohol-acetone

- 20 45.1 gms. of N₁-chlor-N₁-methyl-N-hydroxymethyl-nicotinic acid amide was obtained having a melting point of 160—161° C., the yield amounting to 78% of the theoretical. The new compound is quite soluble in water and alcohol but sparingly soluble in ether, acetone and dioxane.

EXAMPLE 3.

- 30 11.2 Ccs. of neutralised 40% formaldehyde solution were added to a suspension of 35 gms. of N₁-brom-N₁-cetyl-nicotinic acid amide in 200 ccs. of ethanol. The mixture was heated to 30° C. and a solution was formed in a short time. After standing for half-an-hour at 30° C. the solution was allowed to cool whereupon 35 25 gms. of N₁-brom-N₁-cetyl-N-hydroxymethyl-nicotinic acid amide crystallised out. The amide could easily be purified by recrystallisation from alcohol. It melts at 40 219—220° C. with decomposition and is readily soluble in hot water and in the usual organic solvents on heating.

EXAMPLE 4.

- 45 50 Gms. of N₁-methanesulphonate-N₁-octyl nicotinic acid amide of a melting point of 129—130° C. were dissolved with 12 ccs. of a neutralised 39% formaldehyde solution in 500 ccs. of ethanol and 50 heated for an hour to 60° C. The solution was then evaporated to dryness *in vacuo* at 30° C. The slightly yellowish crystalline residue was redissolved in absolute ethanol, the solution was treated with 55 charcoal and the filtrate precipitated with ether. N₁ - methane-sulphonate-N₁-octyl-N-hydroxymethyl-nicotinic acid amide was obtained in fine white crystals which melt at 98° C. The yield was 32.5 gms. 60 corresponding to 59% of the theoretical yield. The new compound is readily soluble in water, ethanol and chloroform, it is insoluble in ether, petroleum ether and benzene.

EXAMPLE 5.

15 gms. of N-hydroxymethyl-nicotinic acid amide were added to a solution of 30 gms. of methanesulphonic acid octyl ester in 150 ccs. of dioxane and heated with stirring to 100° C. for 12 hours. The solution was then evaporated *in vacuo* at 30° C. to a thick consistency and then extracted several times with petroleum ether in order to remove the excess of methanesulphonic acid octyl ester. The residue falls apart to a powdery mass which could readily be reprecipitated with ether from absolute ethanol. 22 gms. of N₁-methanesulphonate - N₁ - octyl-N-hydroxy - methyl-nicotinic acid amide were thus obtained as colourless crystals melting at 98° C. The yield corresponds to 61% of the theoretical yield. The new compound is readily soluble in water, ethanol and chloroform, it is insoluble in ether, petroleum ether and benzene.

EXAMPLE 6.

22 gms. of N₁-chlor-N₁-carboxymethyl-nicotinic acid amide (produced in a manner analogous to that described in Berichte 23 2608) were suspended with 11 ccs. of a neutralised formaldehyde solution in 200 ccs. of ethanol. The whole was heated for an hour to 50° C. and then allowed to cool slowly. Acetone was carefully added and the mixture placed in a cooling cupboard as soon as crystallisation began. After several days 18.3 gms. of N₁ - chlor-N₁-carboxy-methyl-N-hydroxymethyl-nicotinic acid amide had separated, which melts at 120° C. with decomposition. The yield corresponds to 73% of the theoretical yield. The new compound is readily soluble in water and methanol, and is less soluble in acetone, ether and acetic ester.

EXAMPLE 7.

38 gms. of N-hydroxymethyl-nicotinic acid amide were intimately mixed with 23.6 gms. of chloracetic acid and carefully heated to 100° C. The mixture melted within 30 minutes to a clear mass, the melt was then cooled, pulverised, dissolved in ethanol and precipitated with acetone. 41 gms. of N₁-chlor-N₁-carboxy-methyl-N-hydroxymethyl-nicotinic acid amide were obtained which melts with decomposition at 120° C. The new compound is readily soluble in water and methanol and is less soluble in acetone, ether and acetic ester.

EXAMPLE 8.

22 gms. of N₁ - chlor - N₁ - carbamidomethyl-nicotinic acid amide were heated for one hour to 40° C. in 10 ccs. of 40% neutralised formaldehyde solution in 200 ccs. of ethanol. After cooling acetone was added drop by drop to the solution until crystallisation began and the solution

was then placed in ice. After some time 19.8 gms. of N₁-chlor-N₁-carbamido-methyl-N-hydroxymethyl-nicotinic acid amide had crystallised out which melts at 125° C. with decomposition. The yield corresponds to 80% of the theoretical yield. The new compound is moderately soluble in water, readily soluble in ethanol and methanol, and only sparingly soluble in acetone.

EXAMPLE 9.

38 gms. of N-hydroxymethyl-nicotinic acid amide were well mixed with 24 gms. of chloracetamide and cautiously heated to 105° C. The mass fused with evolution of heat. After approximately 30 minutes the melt had become homogeneous. It was then cooled, pulverised and recrystallised from ethanol/acetone. In this way 52 gms. of N₁-chlor-N₁-carbamidomethyl-N-hydroxymethyl-nicotinic acid amide were obtained melting at 126° C. with decomposition. The yield corresponds to 84% of the theoretical yield. The new compound is moderately soluble in water, readily soluble in ethanol and methanol and only very sparingly soluble in acetone.

EXAMPLE 10.

50 gms. of N-hydroxymethyl-nicotinic acid amide were heated with 600 ccs. of dioxane and 120 gms. of *n*-cetyl bromide in the autoclave for 31 hours at 100—110° C. After cooling the solvent was decanted and the partially crystalline residue was recrystallised from ethanol/acetic ester. 122 gms. of N₁-brom-N₁-cetyl-N-hydroxymethyl-nicotinic acid amide were obtained corresponding to a yield of 78.9% of the theoretical. The new compound melts at 219—220° C. and is readily soluble in the heat in the usual organic solvents. It can be purified well by recrystallisation from ethanol.

EXAMPLE 11.

50 gms. of N-hydroxymethyl-nicotinic acid amide were heated with 98.4 gms. of *n*-lauryl bromide and 600 ccs. of dioxane to 100—110° C. for 30 hours in a shaking autoclave. After cooling the crystalline product was sucked off, washed with a little dioxane and then recrystallised from ethanol/acetic ester. 91 gms. of N₁-brom-N₁-dodecyl-N-hydroxymethyl-nicotinic acid amide were obtained corresponding to a yield of 68.5% of the theoretical. The new compound melts at 140—145° C. and is readily soluble in ethanol, hot water and hot dioxane and is insoluble in acetic ester, ether and acetone.

The following compounds can be obtained in analogous manner by the action of formaldehyde:

(a) N₁-methane-sulphonate-N₁-ethyl-N-

hydroxymethyl-nicotinic acid amide from N₁-methane-sulphonate-N₁-ethyl nicotinic acid amide.

(b) N₁-methoxy-sulphonate-N₁-methyl-N-hydroxymethyl-nicotinic acid amide from N₁-methoxy-sulphonate-N₁-methyl-nicotinic acid amide.

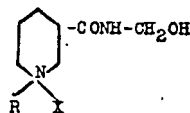
The two above-mentioned compounds can also be prepared from N-hydroxymethyl-nicotinic acid amide and the following components:

(a) Methane-sulphonic acid ethyl ester.

(b) Dimethyl-sulphate.

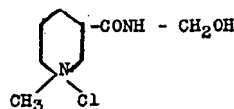
What we claim is:—

1. New chemical compounds of the general formula

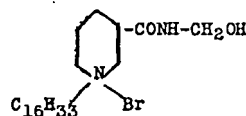


in which R is an alkyl, carboxyalkyl, carbalkoxyalkyl or carbamidoalkyl group containing at most twenty carbon atoms and X is a halogen atom or an alkylsulphonate or alkoxy sulphonate group containing at most six carbon atoms.

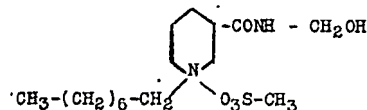
2. The new chemical compound N₁-chlor-N₁-methyl-N-hydroxymethyl-nicotinic acid amide of the formula



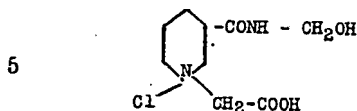
3. The new chemical compound N₁-brom-N₁-cetyl-N-hydroxymethyl-nicotinic acid amide of the formula



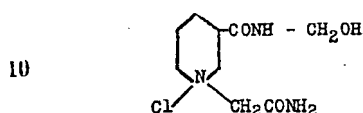
4. The new chemical compound N₁-methane-sulphonate-N₁-octyl-N-hydroxymethyl-nicotinic acid amide of the formula



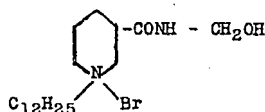
5. The new chemical compound N₁-chlor-N₁-carboxymethyl-N-hydroxymethyl-nicotinic acid amide of the formula:



6. The new chemical compound N₁-chlor-N₁-carbamidomethyl-N-hydroxymethyl-nicotinic acid amide of the formula:



7. The new chemical compound N₁-brom-N₁-dodecyl-N-hydroxymethyl-nicotinic acid amide of the formula:



8. A process for the production of quaternary derivatives of N-hydroxymethyl-nicotinic acid amide which comprises reacting formaldehyde with a compound of the general formula:



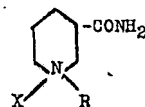
in which R is an alkyl, carboxyalkyl, carbalkoxyalkyl or carbamidoalkyl group containing at most twenty carbon atoms and X is a halogen atom, an alkylsulphonate group or an alkoxysulphonate group containing at most six carbon atoms.

9. A process according to claim 8, wherein formaldehyde is reacted with a N₁-halogen-N₁-alkyl-nicotinic acid amide, the alkyl group whereof contains at most twenty carbon atoms.

10. A process according to claim 8, wherein formaldehyde is reacted with N₁-chlor-N₁-methyl-N-hydroxymethyl-nicotinic acid amide so as to form N₁-chlor-N₁-methyl-N-hydroxymethyl-nicotinic acid amide.

11. A process according to claim 8, wherein formaldehyde is reacted with N₁-brom-N₁-cetyl-nicotinic acid amide so as to form N₁-brom-N₁-cetyl-N-hydroxymethyl-nicotinic acid amide.

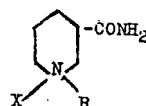
12. A process according to claim 8, wherein formaldehyde is reacted with compounds of the formula



in which R is an alkyl residue containing at most twenty carbon atoms and X is an alkyl sulphonate group containing at most six carbon atoms.

13. A process according to claim 8, wherein formaldehyde is reacted with N₁-methane-sulphonate-N₁-octyl-nicotinic acid amide so as to form N₁-methane-sulphonate-N₁-octyl-N-hydroxymethyl-nicotinic acid amide.

14. A process according to claim 8, wherein formaldehyde is reacted with compounds of the formula



wherein R is a carboxyalkyl, carbalkoxyalkyl or carbamidoalkyl group and X is a halogen atom.

15. A process according to claim 8, wherein formaldehyde is reacted with N₁-chlor-N₁-carboxymethyl-nicotinic acid amide so as to form N₁-chlor-N₁-carboxymethyl-N-hydroxymethyl-nicotinic acid amide.

16. A process according to claim 8, wherein formaldehyde is reacted with N₁-chlor-N₁-carbamidomethyl-nicotinic acid amide so as to form N₁-chlor-N₁-carbamidomethyl-N-hydroxymethyl-nicotinic acid amide.

17. A process for the production of quaternary derivatives of N-hydroxymethyl-nicotinic acid amide which comprises reacting N-hydroxymethyl-nicotinic acid amide with a compound of the formula



wherein R is an alkyl, carboxyalkyl, carbalkoxyalkyl or carbamidoalkyl group containing at most twenty carbon atoms and X is a halogen atom or an alkylsulphonate or alkoxy-sulphonate group containing at most six carbon atoms.

18. A process according to claim 17, wherein N-hydroxymethyl-nicotinic acid amide is reacted with compounds of the formula:



wherein R is an alkyl group containing at most 20 carbon atoms and X is a halogen atom.

19. A process according to claim 17, 10 wherein methyl chloride is reacted with N-hydroxymethyl-nicotinic acid amide so as to form N₁-chlor-N₁-methyl-N-hydroxymethyl-nicotinic acid amide.

20. A process according to claim 17, 15 wherein cetyl bromide is reacted with N-hydroxymethyl-nicotinic acid amide so as to form N₁-brom-N₁-cetyl-N-hydroxymethyl-nicotinic acid amide.

21. A process according to claim 17, 20 wherein N-hydroxymethyl-nicotinic acid amide is reacted with a compound of the formula:



25 wherein R is an alkyl residue containing at most 20 carbon atoms and X is an alkylsulphonate group containing at most 6 carbon atoms.

22. A process according to claim 17, wherein methane sulphonic acid octyl 30 ester is reacted with N-hydroxymethyl-nicotinic acid amide so as to form N-methane-sulphonate-N₁-octyl-N-hydroxymethyl-nicotinic acid amide.

23. A process according to claim 17, 35 wherein N-hydroxymethyl-nicotinic acid amide is reacted with a compound of the formula:



wherein R is a carboxyalkyl, carbalkoxy-alkyl or carbamidoalkyl group containing 40 at most 20 carbon atoms and X is a halogen atom.

24. A process as claimed in claim 17, wherein chloracetic acid is reacted with N-hydroxymethyl-nicotinic acid amide so 45 as to form N₁-chlor-N₁-carboxymethyl-N-hydroxymethyl-nicotinic acid amide.

25. A process according to claim 17, wherein chlor-acetamide is reacted with N-hydroxymethyl-nicotinic acid amide so 50 as to form N₁-chlor-N₁-carbamido-methyl-N-hydroxymethyl-nicotinic acid amide.

26. A process according to claim 17, wherein n-lauryl bromide is reacted with N-hydroxymethyl-nicotinic acid amide so 55 as to form N₁-brom-N₁-dodecyl-N-hydroxymethyl-nicotinic acid amide.

27. A process for the production of quaternary derivatives of N-hydroxymethyl-nicotinic acid amide substan- 60 tially as described with reference to Examples 1, 3, 4, 6 and 8.

28. A process for the production of quaternary derivatives of N-hydroxymethyl-nicotinic acid amide substan- 65 tially as described with reference to Examples 2, 5, 7, 9, 10 and 11.

29. Quaternary derivatives of N-hydroxymethyl-nicotinic acid amide 70 whenever prepared by the process claimed in any of the preceding claims 8 to 28.

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